08 246034

Patent Application for

METHODS AND COMPOSITIONS FOR THE DRY POWDER FORMULATION OF INTERFERONS

Inventors

Robert M. Platz and Linda C. Foster

"Express Mail" mailing label number TB 506 939 61 X US

Date of Deposit May 18, 1994

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Date: 5-18-94 By Patricia K. Parry

20739949

METHODS AND COMPOSITIONS FOR THE DRY POWDER FORMULATION OF INTERFERONS

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates generally to methods and compositions for the dry powder formulation of interferon. More particularly, the present invention relates to the spray drying of interferons (IFNs) to produce dry powder formulations of high potency.

Interferons are cytokines useful in the treatment of a variety of human diseases ranging from cancer to immune system enhancement. Interferons are commonly formulated as isotonic aqueous solutions for parenteral administration. Recently, clinicians have sought alternative routes of administration for interferons more suitable to long term use by patients. Particularly, aerosol formulations of interferons have been produced for pulmonary delivery as described in WO 91/16038. The formulation is dispersed by volatilization of a liquid propellent.

While the pulmonary delivery of interferons shows promise as an alternative to parenteral administration, and may therefore have great clinical utility, the current state of the art, wherein aerosolizable formulations of IFNs, particularly IFN-beta, are produced by lyophilization and subsequent jet milling, produce relatively low potency formulations. It is believed that this is due to the harsh treatment of the protein during the jet milling process wherein high shear forces are applied to the compound in order to produce particles of a diameter suitable for pulmonary delivery, namely less than 10 μm. Further, jet milled dry powders have relatively poor flow characteristics which increases dose variability in dry powder inhaler devices, decreases device efficiency, and increases the cost of powder filling procedures. Since interferons are fairly expensive compounds, it is highly desirable to have formulations of higher potency with improved flow characteristics that can be used with higher efficiency in dry powder inhalers to produce reproducible doses for pulmonary delivery.

2. Description of the Background Art

Methods and compositions for the preparation of solid polypeptide microparticles as a pharmaceutical aerosol formulation are disclosed in WO 91/16038 wherein IFN-beta was prepared in dry powder form by lyophilizing an aqueous solution of IFN and jet milling following lyophilization. The purification of proteins of molecular weight in excess of 12,000, including human IFN is disclosed in U.S. Patent No.: 4,503,035. Low pH pharmaceutical compositions of recombinant IFN-beta are disclosed in WO 89/05158

SUMMARY OF THE INVENTION

One aspect of this invention is an interferon-based dry powder composition for pulmonary delivery, said composition comprising a therapeutically effective amount of interferon in combination with a pharmaceutically acceptable carrier.

Another aspect of this invention is a unit dosage form for pulmonary delivery of interferon, which dosage form comprises a unit receptacle containing the interferon-based dry powder composition of this invention.

A third aspect of this invention is a method of treating a disease state responsive to treatment by interferon, which method comprises administering a physiologically effective amount of the interferon-based dry powder composition to the pulmonary region of the lung of a subject in need thereof.

Still another aspect of this invention is a method for aerosolizing the interferon-based dry powder composition that comprise dispersing an amount of the dry powder composition in a gas stream to form an aerosol and capturing the aerosol in a chamber having a mouthpiece for subsequent inhalation by a patient.

Still another aspect of this invention is a method for preparing the interferon-based dry powder composition that comprises spray-drying an aqueous mixture of the interferon and the carrier under conditions to provide a respirable dry powder.

DESCRIPTION OF SPECIFIC EMBODIMENTS

The present invention is based at least in part on the higher potency and improved flow characteristics of interferon-based dry powder compositions produced by spray drying according to the present invention. Higher potency means that the resulting

interferon-based composition has a higher percentage of physiologically active interferon than compositions prepared by other methods. The compositions of the invention are readily aerosolized and rapidly absorbed through the lungs of a host when delivered by a dry powder inhaler.

DEFINITIONS

In interpreting the claims to the various aspects of this invention, there are several important definitions that should be considered.

The term "interferon" is meant to include the family of naturally-occurring or recombinantly prepared small proteins and glycoproteins (sometimes referred to as cytokines) with molecular weight between approximately 15,000 and 27,000 daltons and having interferon-like activity. Generally, such activity is exerted by binding to specific membrane receptors on a cell surface. Once bound, interferons initiate a complex series of intracellular events that vary among the various interferons. Interferons are useful in the treatment of a variety of human conditions varying from cancer to immune system suppression. Naturally occurring interferons are produced and secreted by cells in response to viral infections and to synthetic and biological inducers. Some interferons are modified versions of the naturally occurring material and are prepared using recombinant DNA technology. Interferon is sometimes abbreviated as "IFN" and shall be so abbreviated in this application. Examples of interferons include, e.g. IFN-alpha-2A recombinant (Roferon® A-Roche Laboratories), IFN-alpha-2B recombinant (Intron® A-Shering), IFN-alpha-N3 human leukocyte derived (Alferon® N-Purdue Frederick), IFN-gamma-1B (Actimmune®-Genentech), IFN-beta recombinant (Betaseron®-Chiron, Berlex), IFN-beta naturally occurring (Feron®-Toray, Japan), and the like. U.S. Patent 4,503,035 issued March 5, 1985 to Pestka and Rubinstein gives examples of human leukocyte IFNs. For purposes of this invention IFN-beta is preferred, particularly naturally occurring IFN-beta.

The term "powder" means a composition that consists of finely dispersed solid particles that are free flowing and capable of being readily dispersed in an inhalation device and subsequently inhaled by a subject so that the particles reach the lungs to permit penetration into the alveoli. Thus, the powder is said to be "respirable." Preferably the average particle size is less than about 10 microns (μm) in diameter with a

relatively uniform spheroidal shape distribution. More preferably the diameter is less than about 7.5 μm and most preferably less than about 5.0 μm. Usually the particle size distribution is between about 0.1 μm and about 5μm in diameter, particularly about 2 μm to about 5 μm.

The term "dry" means that the composition has a moisture content such that the particles are readily dispersable in an inhalation device to form an aerosol. This moisture content is generally below about 10% by weight (%w) water, usually below about 5%w and preferably less than about 3%w.

The term "therapeutically effective amount" is the amount present in the composition that is needed to provide the desired level of interferon in the subject to be treated to give the anticipated physiological response. This amount is determined for each interferon on a case-by-case basis. Guidelines are given hereafter.

The term "physiologically effective amount" is that amount delivered to a subject to give the desired palliative or curative effect. This amount is specific for each interferon and its ultimate approved dosage level. Guidelines are given hereafter.

The term "pharmaceutically acceptable" carrier means that the carrier can be taken into the lungs with no significant adverse toxicological effects on the lungs.

COMPOSITIONS OF THE INVENTION

One aspect of this invention is an interferon-based dry powder composition for pulmonary delivery, the composition comprising a therapeutically effective amount of interferon in combination with a pharmaceutically acceptable carrier.

In general, the compositions of this invention have a higher IFN potency and greater dispersability than other interferon compositions known in the art. In the dry state IFN is an amorphous form. The IFNs suitable for use in the composition of this invention include the various IFN alphas, IFN betas and IFN gammas encompassed by the broad definition of IFN. The IFN alphas and IFN betas are preferred, with IFN beta being particularly preferred. The composition is particularly valuable for naturally occurring IFN beta, for example that available through Toray Corporation in Japan.

A therapeutically effective amount of IFN will vary in the composition depending on the biological activity of the IFN employed and the amount needed in a unit dosage form. Because IFN is so highly active it must be manufactured in a unit basis in

a manner that allows for ready manipulation by the formulator and by the consumer. This generally means that a unit dosage will be between about 0.5 mg and 15 mg of total material in the dry powder composition, preferably between about 2 mg and 10 mg. Generally, the amount of IFN in the composition will vary from about 0.05%w to about 5.0%w. Most preferably the composition will be about 0.2% to about 2.0%w IFN.

The amount of the pharmaceutically acceptable carrier is that amount needed to provide the necessary stability, dispersability, consistency and bulking characteristics to ensure a uniform pulmonary delivery of the composition to a subject in need thereof. Numerically the amount may be from about 95.0%w to about 99.95%w, depending on the activity of the IFN being employed. Preferably about 98%w to about 99.8%w will be used.

The carrier may be one or a combination of two or more pharmaceutical excipients, but will generally be substantially free of any "penetration enhancers." "Penetration enhancers" are surface active compounds which promote penetration of a drug through a mucosal membrane or lining and are proposed for use in intranasal, intrarectal, and intravaginal drug formulations. Exemplary penetration enhancers include bile salts, e.g., taurocholate, glycocholate, and deoxycholate; fusidates, e.g., taurodehydrofusidate; and biocompatible detergents, e.g., Tweens, Laureth-9, and the like. The use of penetration enhancers in formulations for the lungs, however, is generally undesirable because of the epithelial blood barrier in the lung can be adversely affected by such surface active compounds. The dry powder compositions of the present invention are readily absorbed in the lungs without the need to employ penetration enhancers.

The types of pharmaceutical excipients that are useful as carriers in this invention include stabilizers such as human serum albumin (HSA), bulking agents such as carbohydrates, amino acids and polypeptides; pH adjusters or buffers, and the like. These carriers may be in a crystalline or amorphous form or may be a mixture of the two.

It has been found that HSA is particularly valuable as a carrier in that it provides excellent stabilization of IFN in solution.

Bulking agents that are particularly valuable include compatible carbohydrates, polypeptides, amino acids or combinations thereof. Suitable carbohydrates

include monosaccharides such as galactose, D-mannose, sorbose, and the like; disaccharides, such as lactose, trehalose, and the like; cyclodextrins, such as 2-hydroxypropyl-β-cyclodextrin; and polysaccharides, such as raffinose, maltodextrins, dextrans, and the like; alditols, such as mannitol, xylitol, and the like. A preferred group of carbohydrates includes lactose, ~~threhalose,~~ trehalose, raffinose maltodextrins, and mannitol. Suitable polypeptides include aspartame. Amino acids include alanine and glycine, with glycine being preferred.

Additives, which are minor components of the composition of this invention, may be included for conformational stability during spray drying and for improving dispersability of the powder. These additives include hydrophobic amino acids such tryptophan, tyrosine, ~~lucine,~~ leucine, phenylalanine, and the like.

Suitable pH adjusters or buffers include organic salts prepared from organic acids and bases, such as sodium citrate, sodium ascorbate, and the like; sodium citrate is preferred.

The compositions of this invention are prepared as described hereafter.

Unit Dosage Form

Another aspect of this invention is a unit dosage form for pulmonary delivery of interferon, which dosage form comprises a unit dosage receptacle containing an interferon-based dry powder composition, which composition comprises a therapeutically effective amount of an interferon in combination with a pharmaceutically acceptable carrier.

In this aspect of the invention, the composition of this invention (as discussed hereinbefore) is placed within a suitable dosage receptacle in an amount sufficient to provide a subject with IFN for a unit dosage treatment. The dosage receptacle is one that fits within a suitable inhalation device to allow for the aerosolization of the interferon-based dry powder composition by dispersion into a gas stream to form an aerosol and then capturing the aerosol so produced in a chamber having a mouthpiece attached for subsequent inhalation by a subject in need of treatment. Such a dosage receptacle includes any container enclosing the composition known in the art such as gelatin or plastic capsules with a removable portion that allows a stream of gas (e.g., air) to be directed into the container to disperse the dry powder composition. Such containers are

exemplified by those shown in U.S. Patents 4,227,522 issued October 14, 1980; 4,192,309 issued March 11, 1980; and 4,105,027 issued August 8, 1978. Suitable containers also include those used in conjunction with Glaxo's Ventolin Rotohaler brand powder inhaler or Fison's Spinhaler brand powder inhaler. Another suitable unit-dose container which provides a superior moisture barrier is formed from an aluminum foil plastic laminate. The IFN-beta powder is filled by weight or by volume into the depression in the formable foil and hermetically sealed with a covering foil-plastic laminate. Such a container for use with a powder inhalation device is described in U.S. Patent 4,778,054 and is used with Glaxo's Diskhaler® (U.S. Patents 4,627,432; 4,811,731; and 5,035,237). All of these references are incorporated herein by reference.

Method of Treating a Disease State

Another aspect of this invention is a method of treating a condition responsive to treatment by interferon, which method comprises pulmonarily administering to a subject in need thereof a physiologically effective amount of an interferon-based dry powder composition that comprises a therapeutically effective amount of an interferon in combination with a pharmaceutically acceptable carrier.

Conditions that may be treated by the composition of this invention include those conditions that are responsive generally to treatment with IFN. For example, IFN alpha is used to treat hepatitis B and C, Hairy Cell Leukemia, chronic hepatitis Non A, Non B/C and Kaposi's Sarcoma; IFN beta is used to treat multiple sclerosis and hepatitis B and C; and IFN gamma is used to treat chronic granulomatous disease.

The physiologically effective amount needed to treat a particular condition or disease state will depend on the individual, the condition, length of treatment, the regularity of treatment, the type of IFN, and other factors, but can be determined by one of ordinary skill in the medicinal arts. The dosage may range from .25 x 10^6 IU to 50 x 10^6 IU per person per day depending on the prescribing doctor's diagnosis. For example an induction dosage of IFN alpha recombinant (Roferon®A-Roche Laboratories) for treatment of hairy cell leukemia may be 3 x 10^6 IU daily for 16-24 weeks with a maintenance dose of 3 x 10^6 IU three times per week. Other dosage regimes may be determined through clinical trials and reference to the Physicians Desk Reference® for 1994 as supplemented.

It is presently believed that the effective absorption by a host of dry powder interferon according to the present invention results from a rapid dissolution in the ultra-thin (< 0.1 fm) fluid layer of the alveolar lining of the lung. The particles of the present invention thus have a mean size which is from 10 to 50 times larger than the lung fluid layer, making it unexpected that the particles are dissolved and the interferon systemically absorbed in a rapid manner for either local lung or systemic treatment. An understanding of the precise mechanism, however, is not necessary for practicing the present invention as described herein.

The aerosolized interferon-based dry powders of this invention are particularly useful in place of parenteral delivery. Thus, the methods and compositions of the present invention will be particularly valuable in chronic treatment protocols where a patient can self-medicate. The patient can achieve a desired dosage by inhaling an appropriate amount of interferon, as just described. The efficiency of systemic interferon delivery via the method as just described will typically be in the range from about 15% to 50%, with individual dosages (on a per inhalation basis), typically being in the range from about 3 million IU to about 50 million IU during a single respiratory administration. Thus, the desired dosage may be effected by the patient taking from 1 breath to 5 breaths.

Method for Aerosolizing the Powder

Still another aspect of this invention is a method for aerosolizing an interferon-based dry powder composition that comprises a therapeutically effective amount of an interferon in combination with a pharmaceutically acceptable carrier, which method comprises dispersing an amount of the dry powder composition in a gas stream to form an aerosol and capturing the aerosol in a chamber having a mouthpiece for subsequent inhalation by a patient.

A further detailed description of this method is found in pending U.S. Patent Applications Ser. Nos. 07/910,048 and 08/207,472, both of which are incorporated herein by reference.

Preparing the Compositions

Still another aspect of this invention is a method for preparing an interferon-based dry powder composition of this invention that comprises spray-drying an aqueous

mixture of the interferon and a pharmaceutically acceptable carrier having an interferon-stabilizing pH under conditions to provide a respirable dry powder composition.

Spray drying is a process in which a homogeneous aqueous mixture of IFN and the carrier is introduced via a nozzle (e.g., a two fluid nozzle), spinning disc or an equivalent device into a hot gas stream to atomize the solution to form fine droplets. The solvent, generally water, rapidly evaporates from the droplets producing a fine dry powder having particles 1 to 5 μm in diameter. Surprisingly, the protein is not degraded when it is exposed to the hot drying gas, and the interferon powders can be prepared having sufficient purity for pharmaceutical use. An acceptable purity is defined as less than 5% degradation products and contaminates, preferably less than 3% and most preferably less than 1%.

The spray drying is done under conditions that result in substantially amorphous powder of homogeneous constitution having a particle size that is respirable, a low moisture content and flow characteristics that allow for ready aerosolization. Preferably the particle size of the resulting powder is such that more than about 98% of the mass is in particles having a diameter of about 10 μm or less with about 90% of the mass being in particles having a diameter less than 5 μm. Alternatively, about 95% of the mass will have particles with a diameter of less than 10 μm with about 80% of the mass of the particles having a diameter of less than 5 μm.

According to the methods of the present invention, interferon dry powders of higher potency and improved flow characteristics are prepared by spray drying, where, bulk interferon, preferably IFN-beta but suitably other forms of interferon, is prepared in solution to have a concentration from 0.0005% by weight to .02% by weight, usually from .001% to .005%. The solutions may contain a stabilizer to maintain the chemical stability of the IFN-beta in solution such as HSA in a concentration from 0.01% to 1.0% by weight and preferably 0.05% to 0.25% by weight and may contain other material such as a salt or preservative that is present as a result of the preparation of bulk IFN. The solutions may then be sprayed dried in conventional spray drying equipment from commercial suppliers, such as Buchi, Niro, and the like, resulting in a substantially amorphous particulate product.

By minimizing the amount of stabilizer in the solution, high potency IFN powder can be prepared such that the number of inhalations required to deliver even high dosages of IFN can be substantially reduced, often to only a single inhalation.

Interferon dry powders suitable for use in the present invention are substantially amorphous, essentially lacking any crystalline structure. Dry powder interferons are prepared by spray drying under conditions which result in a substantially amorphous powder having a particle size within the above-stated range. According to the methods of the present invention, interferon dry powders of higher potency and improved flow characteristics are prepared by spray drying, where, bulk interferon, preferably IFN-β but suitably other forms of interferon, is first dissolved in a physiologically acceptable aqueous ~~buffer~~ solution, typically a ~~sodium chloride buffer~~ buffered Saline solution having a pH in the range from about 2 to 9. The interferon is dissolved at a concentration from 0.01% by weight to 1% by weight, usually from 0.1% to 0.2%. The solutions may then be spray dried in conventional spray drying equipment from commercial suppliers, such as Buchi, Niro, and the like, resulting in a substantially amorphous particulate product.

The interferon dry powders of the present invention may optionally be combined with pharmaceutical carriers or excipients which are suitable for respiratory and pulmonary administration. Such carriers may serve simply as bulking agents when it is desired to reduce the interferon concentration in the powder which is being delivered to a patient, but may also serve to enhance the stability of the interferon compositions and to improve the dispersability of the powder within a powder dispersion device in order to provide more efficient and reproducible delivery of the interferon and to improve handling characteristics of the interferon such as flowability and consistency to facilitate manufacturing and powder filling.

Such carrier materials may be combined with the interferon prior to spray drying, i.e., by adding the carrier material to the purified bulk solution. In that way, the carrier particles will be formed simultaneously with the IFN particles to produce a homogeneous powder. Alternatively, the carriers may be separately prepared in a dry powder form and combined with the dry powder interferon by blending. The powder carriers will usually be crystalline (to avoid water absorption), but might in some cases be amorphous or mixtures of crystalline and amorphous. The size of the carrier particles may be selected to improve the flowability of the IFN powder, typically being in the

range from 25 μm to 100 μm. A preferred carrier material is crystalline lactose having a size in the above-stated range.

EXPERIMENTAL

Example I

This example sets forth a method of preparing a composition of this invention.

About 50 mL of purified bulk naturally occurring IFN-beta are obtained and thawed. The constitution of the bulk material is as follows.

HSA	2.00 mg/mL
NaCl	0.59 mg/mL
IFN-beta	0.05 mg/mL
Total Solids	2.64 mg/mL

The resulting aqueous mixture is fed to a Buchi Laboratory Spray Dryer under the following conditions to give a composition of this invention:

Temperature of the aqueous mixture	4°C-10°C
Inlet temperature	115°C-125°C
Feed rate	6 mL/min
Outlet temperature	60°C-70°C

Once the aqueous mixture is consumed, the outlet temperature is maintained at about 70°C for about 15 minutes by slowly decreasing the inlet temperature. This provides a secondary drying to give an IFN-based dry powder composition having a water content of less than 3% as measured by a coulombic Karl Fischer method. In this case the composition (%w based on total solids) is constituted as follows:

1.9%w	IFN-beta
98.1%w	Carrier (75.8% HSA, 22.3 NaCl)

Example II

By following the procedure of Example I, but increasing the outlet temperature to 75°C-80°C during the secondary drying stage, one obtains a composition of this invention having less than 1% w/w ~~1%w~~ water.

Example III

This example sets forth a method of preparing a composition of this invention wherein the carrier includes a bulking agent, i.e., mannitol.

Mannitol is dissolved in bulk aqueous IFN-beta described in Example I to give an aqueous mixture having the following constitution:

Mannitol	5.75 mg/mL
HSA	2.00 mg/mL
NaCl	0.59 mg/mL
IFN-beta	0.05 mg/mL
Total solids	8.39 mg/mL

The resulting aqueous mixture is fed to a Buchi Laboratory Spray Dryer under the following conditions:

Temperature of the aqueous mixture	4°C-10°C
Inlet temperature	115°C-125°C
Feed rate	5 mL/min
Outlet temperature	60°C-70°C
Secondary drying - 15 minutes at	70°C

Although the foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity of understanding, it will be obvious that certain changes and modifications may be practiced within the scope of the appended claims.

All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or

patent application was specifically and individually indicated to be incorporated by reference.

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the appended claims.